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Authors

Pignatta, Daniela

Comai, Luca

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Minireview

Parental squabbles and genome expression: lessons from the polyploids

Daniela Pignatta and Luca Comai

Address: Plant Biology and Genome Center, University of California, 451 E. Health Sciences Drive, Davis, CA 95616, USA.

Correspondence: Luca Comai Email: lcomai@ucdavis.edu

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Abstract

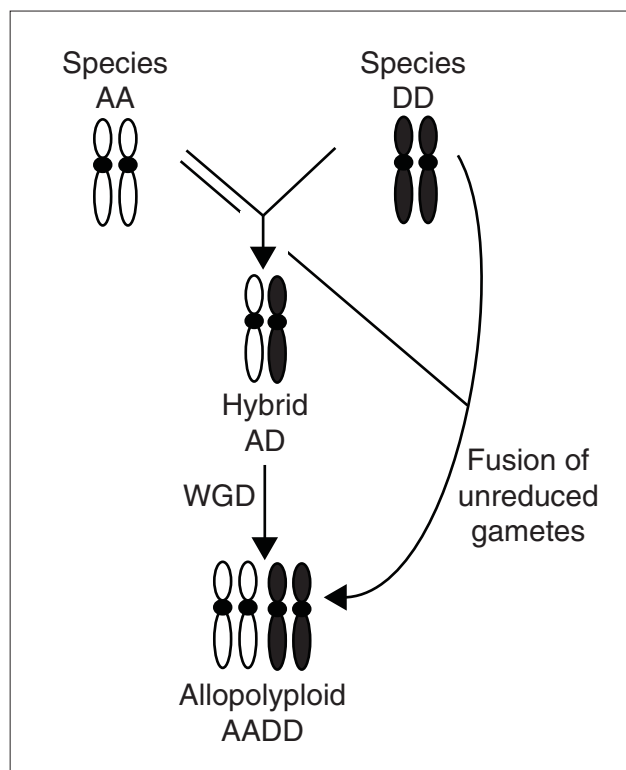
The merger of evolutionarily diverged genomes to form a new polyploid genetic system can involve extensive remodeling of gene regulation. A recent paper in *BMC Biology* provides important insights into regulatory events that have affected the evolution of allopolyploid cotton.

Polyploidy results from multiplication of the entire chromosome set: autopolyploidy when multiplication involves chromosome sets of the same type; allopolyploidy when duplication is either concurrent with or subsequent to hybridization of different species (Figure 1) [1]. In stable allopolyploids parental species-specific chromosome pairing is enforced, and so the two parental genomes are maintained with limited changes through successive generations. Hybridity, the condition in which an organism inherits diverged genomes from each parent, is thus a permanent condition of allopolyploids. Like interspecific hybrids, newly formed allopolyploids display a range of novel phenotypes that are both favorable and unfavorable, but which are overall of questionable fitness. Although it might seem unlikely that these 'freaks of nature' could contribute to the evolutionary race, the remnants of whole-genome duplication in all sequenced plant genomes attests otherwise. Polyploidy - most probably allopolyploidy - recurred multiple times in each analyzed lineage, after which the duplicated gene set fractionated slowly back over evolutionary time to apparent diploidy [2]. Therefore, new allopolyploid species were fit enough to beget the present multitude of seed-plant species.

One question in relation to gene expression in allopolyploids is whether a given gene is expressed at the same levels as expected from the two different genomes - that is, gene expression is additive - or whether one or both of the parental homoeologs, hereafter referred to for simplicity as 'parental alleles', are regulated in a novel fashion (non-additive gene expression). In a recent study published in *BMC Biology*, Rapp *et al.* [3] investigate this question in allopolyploid cotton, and by being able to detect allele-specific expression they have uncovered non-additive expression that would have remained hidden by other methods.

Mechanisms of hybrid incompatibility

To understand the extraordinary contribution of polyploids to diversity, it will be necessary to elucidate the mechanisms that lead to phenotypic variation and how they are modified to achieve adaptation. Among novel hybrid phenotypes, sterility and lethality are deleterious and produce reproductive barriers. Other consequences, such as heterosis or hybrid vigor, can be advantageous. Heterosis makes hybrids perform better than their parents in terms of

**Figure 1**

Mechanisms of polyploid formation. For simplicity, the A and D genomes of the diploid species are represented by only two chromosomes, in white and black, respectively. An allopolyploid (AADD) may form as a result of hybridization of the two species (hybrid AD), followed by whole-genome duplication (WGD). Alternatively, the two diploid species may give rise directly to the allopolyploid by fusion of their unreduced gametes.

increased biomass, size, yield, fertility, resistance to disease, and so on. Hybrids that survive lethality during embryogenesis can display vigorous growth during their later life. Remarkably, heterosis is reinforced by polyploidy: tetraploid hybrids show stronger heterosis than the corresponding diploid hybrids, which helps explain the remarkable success of polyploid plants in evolution [1].

The range of hybrid effects is puzzling and their molecular basis is not understood. All effects, however, must result from genetic variation that has accumulated in the parental lines since their divergence from a common ancestor. So, both favorable and unfavorable effects may derive from fundamentally similar mechanisms.

As early as the 1930s, Dobzhansky and Muller had developed an attractive model to explain incompatibilities between species [4]. They postulated that negative

interactions between evolutionarily diverged genes were the basis for interspecific incompatibilities, leading to reproductive isolation. Molecular examples of such interactions have been described, confirming this genetics-based explanation of hybrid inviability. For example, components of disease-resistance pathways may interact to produce autoimmunity in plants [5], and in flies, components of the nucleoporin complex can display divergence-caused incompatibilities [6]. The type of divergence that produces incompatibility, however, is not limited to structural changes in proteins. Multiple instances involving dosage of interactive factors have also been described, such as the rescue of incompatible crosses by doubling the maternal contribution [7]. Chromosome evolution, such as alternate deletions following duplication of an essential gene, can also lead to incompatibility [8]. In conclusion, multiple genetic changes, including amino acid substitutions in proteins, differential gene regulation, and changes in chromosome structure can result in dramatic consequences upon hybridization. If any of these changes affects master cellular regulators, the consequences will cascade through regulatory pathways, leading to widespread alteration in gene expression.

Changes in genes expression that are mitotically or meiotically heritable, but do not involve DNA changes, are defined as epigenetic. In addition to genetic mechanisms, epigenetic phenomena also play a role in hybridization. A typical epigenetic response involves marking of the affected loci by differential DNA methylation, although other types of chromatin structures are persistent enough to produce epigenetic effects. Nucleolar dominance is one of the first epigenetic phenomena recognized both in plants and animal hybrids, entailing the silencing of one parental set of ribosomal RNA genes, while the other transcriptionally active set produces the nucleolus, which is the site of ribosome assembly [8]. In interspecific crosses, one species is stereotypically dominant, but developmental, genotypic and parental dosage variation can switch the pattern of dominance [9].

Epigenetic mechanisms can contribute to regulation of gene expression in hybrids, either directly or by releasing repression on silenced heterochromatic elements, which can then influence neighboring genes. Large-scale epigenetic resetting was proposed by McClintock as a programmed response to stress ('genomic shock'). Since then, instances of transposon activation in hybrids and of changes consistent with epigenetic mechanisms (for example, RNA interference) have been described. Nevertheless, it is possible to confuse 'unexpected' with 'epigenetic', and so it is important to discriminate genetic and epigenetic causes for the regulatory changes observed in hybrids.

Additive and non-additive gene expression

When the expression of a gene in a hybrid is equal to the average of the two parents, the gene (but maybe not the individual alleles, see below) is said to be expressed in an additive manner; that is, consistent with the original activity of the alleles contributed by each parent (Figure 2). Any deviation from the mid-parental value, that is, either entailing repression or overexpression of one or both parental alleles, is called non-additive expression. A genome-wide microarray analysis in *Arabidopsis thaliana* x *A. arenosa* allopolyploids detected non-additive expression for 8% of genes, with the majority of them being downregulated [10]. The observation that for many non-additively regulated loci, the *A. arenosa* genes were preferentially transcribed in the allopolyploids suggested a phenomenon of 'transcriptional dominance', consistent with the observed nucleolar dominance phenotype in the same cross [10]. The method used in this study could not, however, distinguish the contributions of the parental alleles; dominance was detected by the suppression of genes in the allopolyploid that are strongly expressed in one parent and not in the other. Cases of strong dominance, in which the same amount of mRNA per gene is produced in the allopolyploid because suppression of one parental allele is compensated by the overexpression of the other parental allele, could not be detected.

Now, Rapp *et al.* [3] have addressed this question by using allele-sensitive microarrays to study the regulation of gene expression in cotton allopolyploids, which were formed from diploid parents defined by having an A-type or a D-type genome. They reported widespread 'genomic expression dominance' in which an apparently additive pattern of expression was produced by strong parental allelic bias. The parental origin of the 'winning' alleles was not consistently biased toward one genome, however, but appeared to be a local, gene-by-gene outcome: D alleles in some cases, A alleles in others. Thus, cotton differs from *Arabidopsis* in lacking a strong directional suppression, although a pattern of allelic bias similar to that displayed by cotton could conceivably exist for many *Arabidopsis* gene loci that seemed to be additively regulated.

Cis or trans regulation?

If alleles of both parental genomes display a similar, non-additive response to hybridity, this can be inferred to be due to a change in the regulatory environment of the hybrid, compared to that of either parent, and can be thought of as regulation in *trans*. On the other hand, a downregulation or upregulation of only one parental allele of the pair in the new hybrid environment suggests the existence of functional differences in their *cis*-regulatory regions such as promoters and enhancers. In this case,

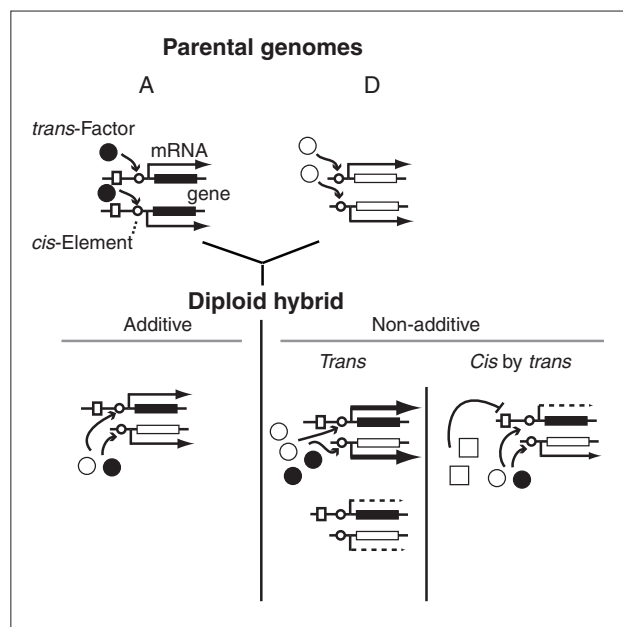


Figure 2

Additive and non-additive gene regulation in hybrids. Alleles from parental genomes A and D (a.k.a. homoeologs) are shown at the top in black and white, respectively. Additive gene expression in the hybrid occurs when the A and D alleles are expressed in the same fashion as they were in the parents (bottom left). Two basic mechanisms can contribute to non-additivity. In *trans*-regulation (center) the hybrid overexpresses (top row) or underexpresses (bottom row) positive regulators that act similarly on both alleles. In *cis* by *trans* regulation (bottom right) the hybrid expresses a negative regulator that acts specifically on one allele because of differences in the *cis*-regulatory regions in the A and D genes. Such a regulator could be novel to the hybrid, or be produced from the unaffected parental genome. In the case illustrated here, a 'D-contributed' repressor (open square) acting on a *cis*-region unique to allele A results in repression of A and thus non-additive expression in the AD hybrid.

exposure to *trans*-acting factors not encountered in the parental species can cause an alteration in the expression of that allele. While both *trans* and *cis* effects can yield non-additive gene regulation, discriminating between the two becomes important in elucidating precise mechanisms (Figure 2).

The observed responses in cotton could have a simple genetic basis. For example, an allele derived from an A parent and displaying suppression may be linked to *cis*-regulatory regions that contain negative regulatory elements not present on the homologous D parent allele (Figure 2). Expression of the cognate repressor, perhaps from D-contributed genes, could selectively shut off the A and not the D allele. In summary, the observation that the RNA output 'per gene' appears additive, while the expression 'per allele' is non-additive, is most consistent with an additive

pattern of expression of *trans*-regulators accompanied by frequent *cis*-divergence of alleles. Of course, as hypotheses for genetic and epigenetic effects emerge and will be tested in future studies, we may be surprised by the causes of these effects.

What is the impact of non-additive gene expression on the evolutionary potential of an allopolyploid? In addition to the obvious remodeling of overall phenotype, the long-term fate of an allele in the allopolyploid, and perhaps of the allopolyploid itself, will depend on its immediate regulation. An allele that is not expressed will escape selection, and evolutionary theory predicts that it will be lost. Alleles that acquire alternative expression patterns after hybridization (A is 'on' in one tissue and 'off' in another, while the D homolog displays the opposite expression pattern) should be likely to undergo subfunctionalization; that is, undergo evolutionary changes that optimize their function for the respective tissue. Thus, the development of hypotheses that explain selective retention of certain ancestral duplicates in diploid genomes should benefit from insights into the mechanisms of hybrid gene regulation [2]. Lastly, alleles that have the potential to participate in strong Dobzhansky-Müller negative interactions should oppose allopolyploid establishment and would be subject to negative selection. In recently formed allopolyploid genomes they might appear as the early singletons, that is, duplicated genes that have decayed to single state through loss of one or the other parental copy. Dobzhansky-Müller alleles that, as demonstrated in the cotton study, are

silenced upon hybridization because of their *cis*-constitution, would increase the fitness of the new allopolyploid, suggesting that certain parental genotypes are more compatible.

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